Hemodynamics associated with breathing through an inspiratory impedance threshold device in human volunteers

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Objective: **Increased negative intrathoracic pressure during spontaneous inspiration through an impedance threshold device (ITD) causes elevated arterial blood pressure in humans. This study was performed to determine whether the acute increase in blood pressure induced by breathing through an ITD is associated with increased stroke volume and cardiac output.**

Design: **Randomized, blinded, controlled trial.**

Setting: **Laboratory.**

Subjects: **Ten women and ten men.**

Interventions: **We measured hemodynamic and respiratory responses during two separate ITD conditions: 1) breathing through a face mask with an ITD (impedance of 6 cm H_2O [0.59 kPa]) and 2) breathing through the same face mask with a sham ITD (control). Stroke volume was measured by thoracic bioimpedance.**

Measurements and Main Results: **Compared with the control condition, ITD produced higher stroke volume (124 ± 3 vs. 137 ± 3 mL; $p = .013$), heart rate (63 ± 3 vs. 68 ± 3 beats/min; $p = .049$), cardiac output (7.69 vs. 9.34 L/min; $p = .001$), and systolic blood pressure (115 ± 2 to 122 ± 2 mm Hg [15.33 ± 0.3 to 16.26 ± 0.3 kPa]; $p = .005$) without affecting expired minute ventilation (6.2 ± 0.4 to 6.5 ± 0.4 L/min; $p = .609$).**

Conclusions: **Breathing with an ITD at relatively low impedance increases systolic blood pressure by increasing stroke volume and cardiac output. The ITD may provide short-term protection against cardiovascular collapse induced by orthostatic stress or hemorrhage. (Crit Care Med 2004; 32[Suppl.]:S381–S386)**

KEY WORDS: respiration; blood pressure; heart rate; stroke volume; cardiac output; peripheral vascular resistance; shock; hypotension; hemorrhage; orthostasis

Hemorrhagic shock remains a leading cause of death worldwide (1–3). One of the challenges to effective treatment is maintenance of vital organ perfusion when intravenous access, intravenous fluids, drug therapies, and surgical intervention are not immediately available (4, 5). Greater negative intrathoracic pressure can be produced by applying resistance during spontaneous inspiration (6–10) and has been associated with elevations in systemic arterial blood pressure and greater organ blood flows in hypovolemic, hypotensive humans and animals (6–13). Building on this concept, an inspiratory impedance threshold device (ITD) was designed to create a vacuum within the chest each time the chest expands during the decompression phase of inspiration (9–11, 14). Recent studies have demonstrated that use of an ITD increases left ventricular end-diastolic volume (9, 15) and end-tidal CO_2 (6, 7, 13) in conditions of circulatory collapse and hemorrhagic shock. These observations raise the possibility that a Starling effect with a subsequent increase in stroke volume and cardiac output represents the underlying mechanism associated with the elevated blood pressure during inspiratory resistance (16). However, stroke volume during resistance breathing with an ITD set at relatively low inspiratory impedance has not been reported in animals or humans. We hypothesized that the acute relative elevation in blood pressure induced by breathing through an ITD would be mechanistically linked with increased stroke volume and cardiac output. This investigation is focused on testing this concept for the first time in humans.

METHODS

Subjects. A total of 20 healthy, normotensive, nonsmoking men (n = 10) and women (n = 10) served as subjects. Descriptive data for the subjects are presented in Table 1. The subjects had not undergone any particular type of exercise training. Because of the potential effects on cardiovascular function, subjects refrained from exercise and stimulants such as caffeine and other nonprescription drugs 48 hrs before testing. During an orien-

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Supported, in part, by a Cooperative Research and Development Agreement between the US Army Institute of Surgical Research and the National Aeronautics and Space Administration (CRDA DAMD17-01-0112) and a grant from the U.S. Army Combat Casualty Care Research Program.

The views expressed herein are the private views of the authors and are not to be construed as representing those of the National Aeronautics and Space Administration, Department of Defense, or Department of the Army.

K. Lurie is a co-inventor of the impedance threshold device and founded Advanced Circulatory Systems to develop the device.

DOI: 10.1097/01.CCM.0000134348.69165.15

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 SEP 2004	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Hemodynamics associated with the human hypertensive response to breathing through an inspiratory impedance threshold device.	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Convertino V. A., Ratliff D. A., Ryan K. L., Doerr D. F., Ludwig D. A., Muniz G. W., Britton D. L., Klah S. D., Fernald K. B., Ruiz A. F., Idris A., Lurie K. G.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**SAR**	**6**	

tation period that preceded each experiment, all subjects were made familiar with the laboratory, the protocol, and procedures. Experimental procedures and protocols were reviewed and approved by the Research Council and Human Use Committee of the US Army Institute of Surgical Research and the Human Investigative Review Board of the Kennedy Space Center for the use of human subjects. Each subject gave written informed voluntary consent to participate in the experiments.

Protocol. Each subject completed two testing sessions that entailed measurements of arterial blood pressures, heart rate (HR), stroke volume (SV), and respiration 1) during breathing through a face mask with an ITD (Advanced Circulatory Systems, Eden Prairie, MN) set at approximately 6 cm H_2O (0.59 kPa) and 2) during a control session (breathing through the same face mask with a sham ITD). Subjects were blinded to the type of ITD used. The order of treatment was counterbalanced so that ten subjects (five men and five women) underwent hemodynamic and respiratory testing during active ITD treatment first while the remaining ten subjects (five men and five women) underwent testing with the sham ITD treatment (control condition) first. There was approximately 1 wk (mean ± SD, 7.2 ± 1.3 days) between each experimental test session. Both testing sessions were initiated at the same time of day for any particular subject.

HR, SV, arterial blood pressures, and tidal volumes were measured as subjects breathed through a face mask with an ITD. The hemodynamic and respiratory measurements were repeated at 5 mins after completion of the 14-min ITD breathing cycle. This protocol represented a complete experimental session. A valve set at 6 cm H_2O (0.59 kPa) of cracking pressure (i.e., the pressure at which the valve opened, allowing air inflow) was chosen because impedance levels as high as 20 cm H_2O (1.96 kPa) were previously proven tolerable and sufficient to increase arterial blood pressure in human subjects (13, 17). Each subject had his or her own disposable face mask. During all experiments, continuous beat-by-beat HR was measured from an electrocardiogram and systolic (SBP) and diastolic (DBP) blood pressures were measured noninvasively by a sphygmomanometric blood pressure monitoring device. Each experimental session was conducted over a period of <60 mins.

Breathing with the ITD. At the beginning of each experimental testing session, each subject breathed spontaneously through an ITD for 14 mins. The ITD comprises a valve that closes when the pressure within the thorax is less than atmospheric pressure and a second valve (termed the safety check valve) that opens at a preset negative intrathoracic pressure (6–8, 14). The ITD was designed to create inspiratory resistance and to therefore increase the magnitude of the vacuum within the chest of a spontaneously breathing subject during inspiration. The ITD was attached to a face mask to ensure that a seal existed between the valve and the skin of the subject's face that was sufficient to eliminate any air leakage (Fig. 1*A*). Because of the greater vacuum within the chest, a larger amount of blood is drawn from the extrathoracic venous system into the chest and heart during inspiration, thereby enhancing cardiac preload (6, 9). Therefore, use of the ITD results in an immediate increase in arterial blood pressure (6, 7, 9, 12, 13, 15). There is little resistance during exhalation.

Measurement of Ventilatory Response to ITD Breathing. After the initial 3 mins of ITD breathing, minute ventilation (in liters per minute) was measured from the additive inspiratory flow for 1 min with an Interface Associates (model VMM 402, Laguna Niguel, CA) turbine transducer (Fig. 1*B*). Inspiratory impedance was measured during the same time interval using an MKS (PDR-C-1C, Andover, MA) pressure transducer between the ITD–patient mask interface (Fig. 1*B*). The analog waveform was recorded on a Gould (Eastlake, OH) strip-chart recorder, and the change in pressure (negative intrathoracic pressure) was measured in centimeters of H_2O. Respiratory rate (in breaths per minute) was measured by counting the negative pressure deflections occurring on the strip chart during the 1-min time period. Tidal volume (in liters) was calculated by dividing minute ventilation by respiratory rate.

Hemodynamic Measurements. Continuous HR was measured with a Hewlett-Packard monitoring system from a standard electrocardiogram. SBP and DBP were measured noninvasively with an automated sphygmomanometer blood pressure measurement device. Mean arterial pressure was calculated by dividing the sum of SBP and twice DBP by three. Beat-to-beat SV was measured noninvasively using thoracic electrical bioimpedance with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC). The thoracic electrical bioimpedance technique is based on the resistance changes in the thorax to a low-intensity (4 mA), high-frequency (70 kHz) alternative current applied to the thorax by two outer-surface electrodes placed at the root of the neck and two surface electrodes placed at the xiphoid process at the midaxillary line. The R-wave of the electrocardiogram was taken as a landmark to average dZ/dt waveforms over ten cardiac cycles that were recorded in 20 secs at the beginning of minute 4 of each measurement period. SV measured during and at 5 mins after ITD breathing was determined as

Table 1. Subject group descriptive data

	Women (n = 10)	Men (n = 10)
Age, yrs	32 ± 4	33 ± 4
Height, cm	167 ± 2	177 ± 1
Weight, kg	63.8 ± 2.5	78.8 ± 2.9
Heart rate, beats/min	66 ± 3	61 ± 3
Systolic blood pressure, mm Hg	110 ± 3	120 ± 3
Systolic blood pressure, kPa	14.6 ± 0.4	16.0 ± 0.4
Diastolic blood pressure, mm Hg	71 ± 2	75 ± 3
Diastolic blood pressure, kPa	9.46 ± 0.3	75 ± 0.4

Values presented as mean ± SE.

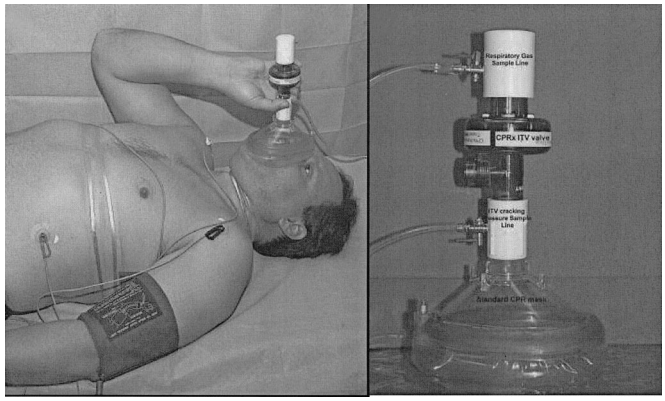

Figure 1. Photographs of the impedance threshold device (ITD) alone and applied to a subject. *Left*, illustration of the ITD placement on a subject instrumented for measurement of heart rate (electrocardiogram), blood pressure (cuff), and stroke volume (electrical impedance electrodes on the neck and thorax). *Right*, illustration of the valve connected to a face mask and sensors for measurement of ventilatory volume/rate and inspiratory pressure.

the average SV from the ten cardiac cycles. Ventricular SV was determined with the partly empirical formula: SV (in milliliters per beat) $= p \times (L/Z_o)^{-2} \times LVET \times (dZ/dt)_{min}$, where p (in ohm-centimeters) is the blood resistivity, a constant of 135 ohm-cm (1.35 ohm-m) *in vivo*; L (in centimeters) is the mean distance between the inner pick-up electrodes; Z_o (in ohms) is the mean baseline thoracic impedance; LVET (in seconds) is the left ventricular ejection time; and $(dZ/dt)_{min}$ (in ohms per second) is the height of the dZ/dt peak (Z-point) measured from the zero line. Most investigators who measured SV with thoracic electrical bioimpedance have reported correlation coefficients of 0.70–0.93 in comparison with thermodilution techniques (18). Cardiac output (CO) was calculated as the product of HR and SV. Total systemic peripheral resistance (TPR) was calculated by dividing mean arterial pressure by CO, and is expressed as peripheral resistance units (in mm $Hg \cdot min^{-1} \cdot L^{-1}$).

Statistical Analysis. The statistical analysis was a standard two group (men, women) by two treatment (6 cm H_2O ITD, control) by two time periods (during, 5 mins after) mixed-model analysis of variance. The model was mixed in the sense that subjects were nested within groups by sex and crossed with treatments and time (i.e., one between-subjects factor [sex] and two within-subjects factors [treatment and time]). To simplify the statistical analysis and make it more interpretable, separate statistical models were constructed for measurements taken during ITD breathing and 5 mins after the cessation of ITD breathing. All main effects and subsequent interactions were analyzed across six dependent effects (SBP, DBP, HR, SV, CO, TPR). Exact *p* values were calculated for each independent effect and reflect the probability of obtaining the observed or greater effect given only random departure from the assumption of no effects. Orthogonal polynomials (i.e., dose-response modeling) or independent contrasts were constructed in the event of statistical differences associated with the main effect of the treatment (i.e., inspiratory impedance level). Standard errors are raw measures of variation about the specific treatment group mean. These standard errors do not reflect variability specific to the factors being tested or the variability associated with statistical tests and subsequent *p* values given in the text.

RESULTS

Descriptive Data. Average and SE baseline values for age, height, weight, HR, and blood pressures for women and men are presented in Table 1. Male and female groups were matched for age. Subjects showed the expected and well-established differences between sexes on height, weight, HR, and blood pressure. For HR and blood pressure, all values were within established normal limits.

ITD and Sex Effects. Sex did not influence the responses of SBP ($F = 0.348$; $p = .563$), DBP ($F = 0.016$; $p = .902$), HR ($F = 0.845$; $p = .370$), SV ($F = 2.894$; $p = .106$), CO ($F = 0.321$; $p = .578$), TPR ($F = 0.030$; $p = .864$), minute ventilation ($F = 0.084$; $p = .776$), or tidal volume ($F = 0.296$; $p = .593$) across treatment during either spontaneous breathing through the ITD or control experimental conditions. Women (11 breaths/min) had a slightly higher respiratory rate than men (9 breaths/min) ($F = 5.174$; $p = .035$) during ITD breathing. Five minutes after spontaneous breathing on the ITD was terminated, SBP, DBP, HR, SV, CO, and TPR were statistically similar (*F* values of <0.415; *p* values of $>.527$) across experimental conditions. Based on these analyses, the data were combined and analyzed as a sample size of 20.

Respiratory Effects of Spontaneous Breathing on an ITD. Average peak negative airway pressure of -9.4 ± 0.3 cm H_2O (-0.92 ± 0.03 kPa) was generated during spontaneous breathing on the ITD. There was no main treatment effect ($F = 0.271$; $p = .609$) on minute ventilation during spontaneous breathing through the ITD (6.5 ± 0.4 L/min) compared with breathing through the sham device (6.2 ± 0.4 L/min). However, tidal volume was higher ($F = 10.05$; $p = .005$) and respiratory rate was lower ($F = 8.084$; $p = .011$) during spontaneous breathing through the ITD (0.86 ± 0.04 L and 9 ± 1 breaths/min, respectively) compared with breathing through the sham device (0.67 ± 0.04 L and 10 ± 1 breath/min, respectively).

Hemodynamic Effects. Mean ($\pm$SE) SBP, DBP, HR, SV, CO, and TPR data during and 5 mins after the cessation of spontaneous breathing through the ITD are presented in Figure 2. There was a large main treatment effect of spontaneous breathing through the ITD on SBP, HR, SV, CO, and TPR (*F* values of >4.481; *p* values of $<.049$). There was no statistically distinguishable treatment effect of spontaneous breathing through the ITD on DBP or minute ventilation. Five minutes after spontaneous breathing on the ITD was terminated, all hemodynamic variables were statistically similar (*F* values of <0.415; *p* values of $>.527$) across experimental conditions (Fig. 2).

DISCUSSION

One of the primary mechanisms that contribute to severe hypotension and ultimately shock after an acute hemorrhage is the reduction in circulating blood volume and subsequent reduction in cardiac filling and SV (19). Therefore, any therapeutic approach that is designed to increase venous return and SV without causing hemodilution should be an effective therapy for the acute treatment of massive blood loss. The application of resistance during spontaneous inspiration has been shown to cause an immediate increase in arterial blood pressure when applied in different clinical models associated with significant life-threatening hypotension (6, 7, 9–13). The concept by which the ITD functions to increase blood pressure is based on the mechanics of producing a greater vacuum within the thorax during each inspiration, which subsequently may increase venous return and preload to the heart (6, 7, 9, 10). We therefore hypothesized that the elevation in arterial blood pressure induced by application of respiratory resistance (i.e., spontaneous breathing through an ITD) results from an increase in SV and CO. To test this hypothesis, we measured SV in normovolemic, normotensive human subjects during spontaneous breathing through an ITD. Our data confirmed that application of the ITD increased SBP in a manner similar to that previously reported (6, 7, 9–13, 15). A new finding of the present investigation was that the elevation in blood pressure induced by spontaneous inspiration on an ITD was mechanistically associated with an increase in SV and CO.

An increase in SV and CO during spontaneous breathing against high resistance pressures (68–88 cm H_2O [6.67–8.63 kPa]) has been reported previously (16). Because of the extraordinarily high resistance, Coast et al. (16) suggested that the increased CO was a result of greater energy demand required for the work of breathing. Our data are unique in demonstrating that a relatively low inspiratory resistance can increase CO and blood pressure with no effect on metabolic demand because the average ($\pm$ standard error) oxygen uptake in ten subjects during 6 cm H_2O (0.59 kPa) of ITD breathing (247 ± 17 mL/min) was not statistically different from that of 228 ± 14 mL/min during breathing on the sham device (unpublished data). Breathing through the ITD was well tolerated by our

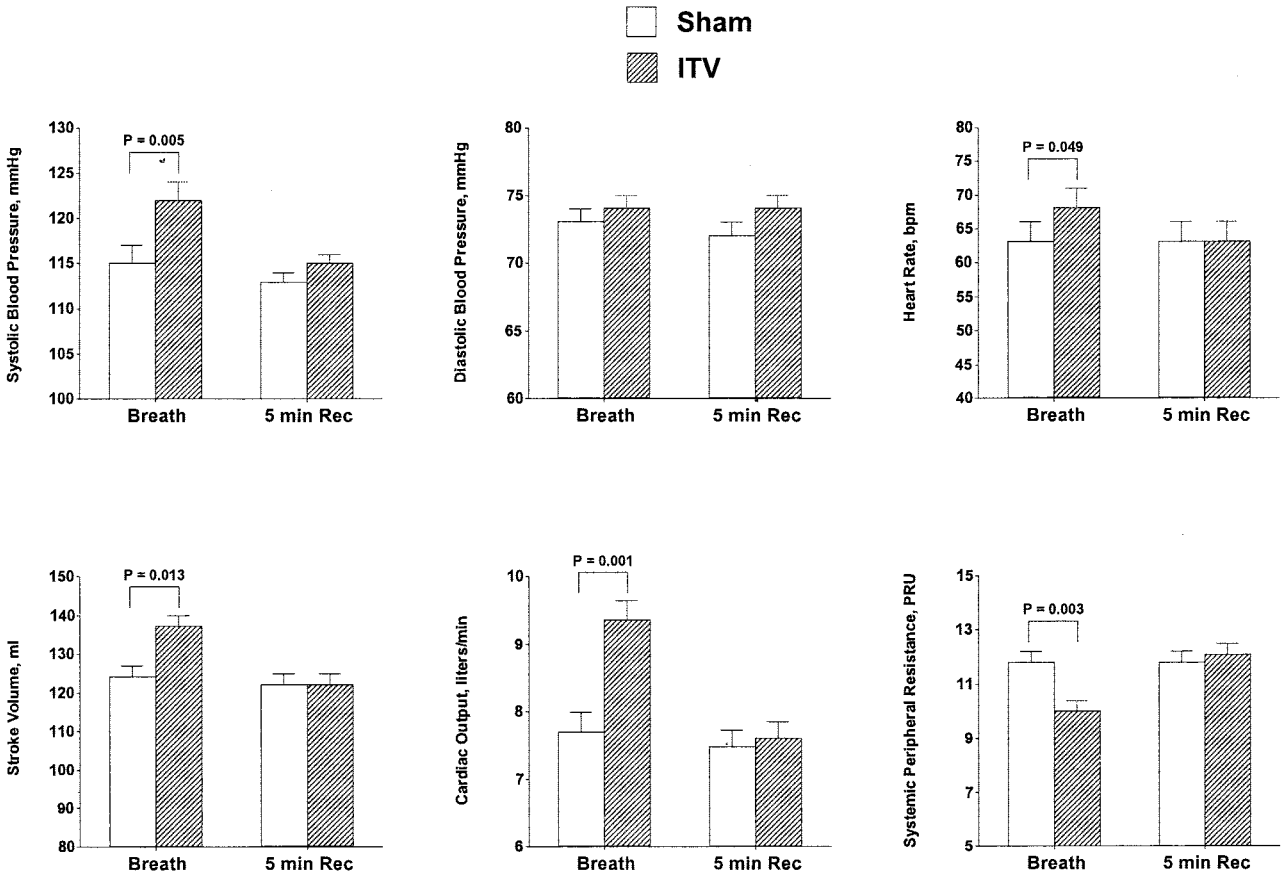

Figure 2. Systolic and diastolic blood pressures, heart rate, stroke volume, cardiac output, and total peripheral vascular resistance during (*Breath*) and after (*5-min Rec*) spontaneous breathing on the impedance threshold device (*ITV*) at 0 cm H_2O resistance (sham control, *open bars*) and 6 cm H_2O (0.59 kPa) resistance (*lined bars*). *Bars* and *lines* represent mean ± 1 SE, respectively (n = 20). *bpm*, beats per minute; *PRU*, peripheral resistance units.

subjects. In light of the statistically similar effects on ventilatory mechanics (volume and rate) and oxygen uptake during breathing on the ITD and sham devices, our results suggest that the application of an ITD to patients in a clinical setting could provide a tolerable therapeutic approach for acute treatment of life-threatening hypovolemia or hypotension.

In addition to an increased SV, an unexpected elevation in HR during spontaneous breathing on the ITD also contributed to higher CO and SBP. Because of the elevation of arterial blood pressure during inspiratory resistance, we had anticipated a bradycardic response mediated by arterial baroreflex feedback control, but ITD breathing actually elicited a tachycardic response in the face of rising arterial blood pressure. Although this tachycardic response seems contraindicated, it is similar to the concurrent elevation in HR and arterial blood pressure responses observed during physical exercise when increased negative intrathoracic pressures are associated with resetting of the cardiac baroreflex stimulus–response relationship to a higher operating range (20, 21). We also found that the elevated HR response during ITD breathing was associated with a resetting of the baroreflex to a higher operating range in our subjects (17). Thus, the increase in CO elicited by spontaneous breathing on the ITD involves mechanisms that contribute to elevations in both SV and HR.

TPR was significantly lower during spontaneous inspiration on the ITD compared with the control condition. This may be expected in light of the evidence that a linear stimulus-response relationship exists between SV and sympathetic nerve activity (22, 23). Thus, as cardiac filling, SV and blood pressure decrease under conditions of central hypovolemia, a reflex increase in sympathetic nerve activity to vascular smooth muscle results in a compensatory elevation in peripheral resistance in an attempt to maintain blood pressure. Although we did not measure sympathetic nerve activity in the present investigation, it is likely that the increases in SV and arterial blood pressure, either individually or collectively, caused by breathing through an ITD in our subjects probably reduced sympathetic nerve activity to the vasculature. This compensatory response of the peripheral vascular resistance could provide two important mechanisms of protection if applied during hemorrhage. First, a lower relative vasoconstriction would function to increase perfusion of vital organs and subsequently delay ischemic injury to tissues. Second, the ability to rely on less peripheral vascular resistance for a given blood loss would provide a greater capacity for vasoconstrictive reserve to defend against hypotension and cardiovascular collapse (24). Future experiments are necessary to test this intriguing hypothesis.

Although modest (7 mm Hg [0.93 kPa]), the magnitude of the average acute elevation in SBP observed in our subjects may be important in that it occurred in healthy normovolemic, normotensive subjects in the supine position, which optimizes venous return. Under these conditions, venous return is optimal. We

Breathing with an impedance threshold device at relatively low impedance increases systolic blood pressure by increasing stroke volume and cardiac output.

hypothesize that even larger elevations in CO and SBP may be produced by spontaneous resistance breathing during conditions such as hemorrhage or orthostasis, when venous return is compromised. This hypothesis is currently being tested using ITD application in human models of central hypovolemia.

Previous investigations have revealed greater risks to cardiovascular collapse during acute central hypovolemia in women compared with men (25, 26). Specifically, a lesser capacity to defend SV, CO, and blood pressure during central hypovolemia was associated with earlier onset of orthostatic hypotension (26) and circulatory collapse (25) in women. We were therefore interested in whether the SV, CO, and blood pressure responses during breathing on an ITD would be different between women and men. Because our subject population was composed of 50% men and 50% women, we had the opportunity to examine the influence of sex on the hemodynamic responses to inspiratory resistance. Like previous studies, we observed that our female subjects had higher average HRs and lower blood pressures than their male counterparts. More importantly, both male and female subjects in our study demonstrated similar elevations in SV, CO, and SBP during increased inspiratory resistance. Therefore, we conclude that application of an ITD is equally effective for enhancing the hemodynamic mechanisms associated with elevation in blood pressure in a population of subjects at higher risk for cardiovascular collapse.

In summary, we demonstrated that the elevation in blood pressure induced by spontaneous breathing through an ITD (i.e., increased resistance) was associated with an increase in CO and a decrease in TPR. The higher CO resulted from greater SV and HR. Both the increase in systemic blood flow and less peripheral vasoconstriction could contribute significantly to maintaining adequate blood perfusion to vital organs in conditions of acute central hypovolemia.

Potential Limitations. There are several limitations to these studies on the ITD in human volunteers. First, we have not yet measured work of breathing. Although oxygen consumption was found to be similar when the subjects breathed through either a sham or an active ITD, it will be important to quantitate the amount of work needed to generate the increase in observed SV. In addition, we do not know how long a person can breath through an ITD with a cracking or opening pressure of 6 cm H_2O (0.59 kPa). In preliminary studies, normal volunteers have easily worn a face mask with an attached ITD for more than an hour. It also remains unclear what kind of normal autoregulatory changes may take place with prolonged use of the ITD. Third, the volunteers who used the ITD were not sick, and it remains unclear whether the ITD will be tolerated by sick patients. Finally, the cracking or opening pressure was fixed in the current version of the ITD. It may be that different individuals will benefit more from ITDs with different or variable cracking pressures. As such, there are a number of potential unanswered questions related to ways to optimize the patient-powered thoracic pump mechanism that underlies the function of the ITD.

Clinical Implications. The results of this investigation are relevant to the application of the ITD during hemorrhagic shock. Death after severe hemorrhage develops secondary to profound hypotension and vital organ ischemia. In the absence of a critical central blood volume, SV and CO are decreased and hypotension ensues. In such medical emergencies, rapid restoration of blood pressure is essential to maintain vital organ function. Therefore, any countermeasure that is designed to increase any one or a combination of these hemodynamic factors should provide some protection against the development of cardiovascular collapse (i.e., circulatory shock). At the present time, there are no clinical therapies, with the exception of intravenous fluids and intravenous vasopressor drugs, that acutely increase CO and blood pressure in states of hypovolemic hypotension. Intravenous access and fluids, however, are not always readily available. The results of the present investigation suggest that application of an ITD during the early stages of controlled hemorrhage may rapidly restore central blood volume, CO, and blood pressure by transforming the thorax into a more active vacuum. Application of an ITD might therefore be used to "buy time" until intravenous access is obtained and fluid resuscitation is begun or as an adjunct to conventional resuscitative therapy. Thus, the conceptual application of an ITD during hemorrhage may provide a critical bridge to more definitive repair of the primary injury and ultimate survival.

ACKNOWLEDGMENTS

We thank the subjects for their cheerful cooperation, Barry Slack and Robert Cummings for their engineering and technical assistance during the experiments, Cathy DiBiase for her assistance with medical monitoring of the subjects during the experiments, Jaqueline Crissey for assistance with data collection, and the participation of the 2002 NASA Space Life Sciences Training Program for their assistance in data collection and analysis.

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